REMARKS

Claims 1-20 are pending in this application. Claims 2, 4, 8, 9, and 12-20 have been withdrawn as being directed to a non-elected invention. Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1, 3, 5-7, 10 and 11 are rejected under 35 U.S.C. § 103(a) for obviousness over Deboer (U.S. Patent No. 5,633,076; hereinafter "Deboer"), Clark (U.S. Patent No. 5,32,775; hereinafter "Clark"), or Lubon (U.S. Patent No. 5,831,141; hereinafter "Lubon") in view of Morinaga et al. (PNAS 80:4604-4608; 1983; hereinafter "Morinaga") and Bennett (Breast Cancer Res. Treatment 45:169-179, 1997; hereinafter "Bennett"). By this reply, Applicants address each of the Examiner's rejections.

Information Disclosure Statement

Applicants note that the reference Hooper et al. (*Biological Activities of Alpha$_1$-Fetoprotein*, eds. Mizejewski et al. 1:153-165 (1987)), which was included with the Information Disclosure Statement and PTO 1449 filed by Applicants on May 1, 2002, was not initialed by the Examiner as having been made of record when the PTO 1449 was initialed by the Examiner and returned to Applicants on March 22, 2005. Accordingly, Applicants respectfully request that the Examiner confirm that this reference has been made of record by placing her initials next to this reference on the enclosed copy of the previously initialed PTO 1449 form, which is provided herewith for the Examiner's convenience.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states:

> Claims 10 and 11 remain rejected...because the specification, while being enabling for a method of producing a rHuAFP that is secreted in the milk of a transgenic non-human mammal wherein the non-human mammal is made by introducing the transgene into cells of an embryo and for a method of producing a rHuAFP that is secreted in the milk of a transgenic mouse wherein the mouse is made by introducing the transgene into cells of an embryo or into mouse ES cells, does not reasonably provide enablement for any such mammal made using any cell type or a transgenic human made using any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use

the invention commensurate in scope with these claims. (Office Action, pp. 2-3.)

In addition, the Examiner states that the Declaration of Edward J. Stewart, which was submitted with the Reply to Office Action, dated September 22, 2005 (the "Prior Reply"), in support of the enablement of claims 10 and 11 was not considered because it was submitted unsigned (Office Action, pp. 4-5).

In response to the present rejection of claims 10 and 11, and as evidence that the invention recited in present claims 10 and 11 is enabled, Applicants now provide a signed copy of a Declaration of Edward J. Stewart and respectfully request that the Examiner reconsider the present rejection in view of the Declarant's remarks. First and foremost, Applicants again point to ¶ 4 of the Declaration, wherein Mr. Stewart attests that scientists working under the direction of the inventors used methods disclosed in the specification and known in the art to successfully produce several transgenic mice and goats capable of expressing rHuAFP and secreting it into their milk. As was discussed in the Prior Reply, ¶¶ 5-7 of the Declaration confirm that several transgenic mice were generated using the method taught on page 13, lines 10-15, of the specification, while seventeen transgenic goats were generated using somatic cells and nuclear transfer methods referenced in Applicants' specification on page 14, lines 4-8, and known in the art prior to Applicants' filing date.

The Declaration also includes Exhibits A-D, which were previously submitted with the Prior Reply. Exhibits A-D include a photograph of "Merri," a transgenic founder goat expressing rHuAFP in its milk, which was made according to the methods disclosed in the specification. Exhibit B is a photograph confirming that the genotype of the transgenic founder goat, Merri, now includes the rHuAFP transgene, which has been amplified by PCR, based on its presence in blood and ear tissue. Exhibit C is a photograph of a Southern blot demonstrating that Merri contains two copies of the HuAFP transgene in a diploid genome, thereby ruling out any gross transgene rearrangement. Finally, Exhibit D is a photograph showing that the HuAFP transgene integrated at a single site on the "q" terminal end on a mid to large sized autosomal chromosome, as determined by fluorescent *in situ* hybridization (FISH). As is apparent from the enclosed Exhibits A-D, the methods disclosed in the specification and known in the art can be successfully used to produce transgenic animals

capable of expressing rHuAFP and secreting it into their milk.

Applicants also direct the Examiner to ¶ 7 of the Declaration, which attests that the expression level of rHuAFP in transgenic goats ranged from 170 mg/L to 700 mg/L. Applicants provide Exhibit E, which shows the expression level of rHuAFP over a nine month period in 15 rHuAFP-expressing transgenic goats. Furthermore, ¶ 8 of the Declaration states that the high level of rHuAFP expression demonstrated by the transgenic goats far surpasses the level of expression obtained using other expression systems and one of skill in the art would not have expected this level of rHuAFP expression in a transgenic mammal.

Because the statements and evidence provided in the Declaration of Edward J. Stewart clearly demonstrate that transgenic mammals expressing and secreting rHuAFP in their milk can be and, in fact, were successfully produced using the methods taught in the present specification and generally known in the art, and thus that one skilled in the art can successfully practice the full scope of present claims 10 and 11, Applicants respectfully request that the rejection of claims 10 and 11 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1, 3, 5-7, 10, and 11 are rejected under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett. The Examiner states:

> It was the general state of the art as demonstrated to by Deboer, Clark and Lubon to use a transgenic non-human mammal as a bioreactor to produce large quantities of any protein of interest. The only elements lacking from any of these references, alone or in combination, is the sequence encoding AFP and motivation to use the sequence in the techniques of any of Deboer, Clark and Lubon...Bennett is relied upon solely for the motivation to apply the teachings of Deboer, Clark and Lubon to the teachings of Morinaga of the AFP gene sequence. (Office Action, pp. 6-7.)

Applicants respectfully traverse the rejection of claims 1, 3, 5-7, 10, and 11.

As was discussed in the Prior Reply, none of Deboer, Clark, or Lubon, either alone or in combination, teaches or suggests the subject matter of independent claims 1, 3, 6, and 10, and claims dependent therefrom, which is directed to a rHuAFP transgene, a transgenic non-human mammal that expresses and secretes rHuAFP into its milk, milk of a transgenic non-human

mammal that contains rHuAFP, and methods of producing rHuAFP by using a transgenic non-human mammal to express and secrete rHuAFP into its milk, respectively. Morinaga and Bennett also fail to teach, suggest, or motivate the skilled artisan to produce rHuAFP in a transgenic mammal's milk. The Examiner states that "[w]hile the teachings of Bennett may be limited to producing rHuAFP using *E. coli*, no more is necessary" (Office Action, p. 7). For the reasons discussed below, the limited disclosure of Bennett is not sufficient to motivate the skilled artisan to move away from the *E. coli* system of Bennett to a transgenic mammalian expression system, as is disclosed by DeBoer, Clark, or Lubon.

No Motivation to Express rHuAFP in Transgenic Mammals

The Examiner states that "Bennett provided the motivation that made AFP a protein of interest...[and] Morinaga taught the AFP gene sequence necessary to apply the techniques of DeBoer, Lubon, and Clark to fulfill the motivation of Bennet [sic]" (Office Action, p. 7). The Examiner's conclusion of sufficient "motivation" based on Bennett is misguided. Bennett provides no teaching or suggestion to express rHuAFP in transgenic mammals. In the absence of any suggestion to express rHuAFP in transgenic mammals, there is no motivation to combine the cited references, and thus, a *prima facie* case of obviousness under 35 U.S.C. § 103 has not been established.

The M.P.E.P. § 2143.01 states:

> There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, *however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.*). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). (Emphasis added.)

As the Federal Circuit recently observed:

> A critical step in analyzing the patentability of claims pursuant to section 103 (a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by prior art references and the then-accepted wisdom in the

> field...Most if not all inventions arise from a combination of old elements... Thus, every element of a claimed invention may often be found in the prior art...However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention...Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citations omitted).

"Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 880, 45 USPQ2d 1977, 1981 (Fed. Cir. 1998). "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Id.* Otherwise, "rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). To avoid hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires an examiner to show a motivation to combine the references that create the case of obviousness. *Id.* That is, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* (emphasis added). This the Examiner has not done.

The Nature of the Problem to be Solved

The Examiner states that "Bennett provided the motivation that made AFP a protein of interest...," and this alone, the Examiner concludes, provided the necessary motivation to combine the cited references to establish a *prima facie* case of obviousness against claims 1, 3, 5-7, 10, and 11 (Office Action, p. 7). Bennett does not provide the motivation advocated by the Examiner because Bennett had already solved the problem

of producing large quantities of rHuAFP by using an *E. coli* expression system. Thus, Bennett provides no motivation to look any further.

Bennett sought to produce substantial quantities of biologically active rAFP for use in understanding the biological function of AFP, namely the therapeutic potential of AFP as a regulator of breast cancer growth (see Abstract and p. 170). Bennett solved this problem by producing substantial quantities of rAFP in *E. coli*. Bennett unequivocally indicates that the *E. coli* expression system addresses all of the problems associated with establishing sufficient quantities of rAFP, stating that the therapeutic effects of AFP "can now be explored in greater depth with the availability of large quantities of functional rAFP" (see p. 178; emphasis added). By indicating that the present *E. coli* expression system satisfied all of the requirements for further studies using AFP, Bennett guides the skilled artisan towards the use of an *E. coli* expression system alone; Bennett does not motivate the skilled artisan to look beyond an *E. coli* expression system to other expression systems, such as a transgenic mammal expression system.

The Teachings of the Prior Art

Bennett, as the primary reference relied upon by the Examiner for a teaching to produce rHuAFP in transgenic mammals, does not convey any sense that one should seek to express rAFP in any expression system other than an *E. coli* expression system. In fact, Bennett confirms that rAFP expression in *E. coli* is preferred over other expression systems, stating that "for the first time large quantities of pure, homogeneous, functional rAFP will enable systematic study of [the biological function of AFP]" (see page 178, col. 1). Bennett further motivates one to employ the *E. coli* expression system only, stating that production of rhAFP "where it is the only human protein and [it] is in an environment where post-synthetic modifications are absent" removes difficulties in determining the activity of proteins, such as AFP (see p. 176, col. 2). Given Bennett's clear preference for the *E. coli* expression system, one skilled in the art would not be motivated to pursue the expression of rHuAFP in transgenic mammals according to the method of present claims 10 and 11, to prepare the compositions of present claims 1, 6,

and 7, or to produce a transgenic mammal as recited in present claims 3 and 5. Thus, the prior art relied upon by the Examiner fails to provide any motivation to produce rHuAFP in transgenic mammals.

The Knowledge of Persons of Ordinary Skill in the Art

As is discussed above, the level of skill in the art cannot be relied upon to provide the suggestion to combine references (M.P.E.P. § 2143.01). Thus, even though Deboer, Clark, and Lubon describe the expression of recombinant proteins other than rHuAFP using transgenic mammals, this knowledge is insufficient to provide a motivation to express rHuAFP specifically, even when combined with Morinaga and Bennett, because none of the references, either singly or in combination, suggest the desirability of making the specific combination that was made by Applicants (*see In re Kotzab*, *supra*). As is discussed above, Bennett fails to teach or suggest the expression of rHuAFP in transgenic mammals and, in fact, Bennett encourages the skilled artisan to look no further than expression in *E. coli*. Morinaga, the final reference cited by the Examiner in the present rejection, also lacks any teaching that would motivate the skilled artisan to seek the expression of rHuAFP using the expression system disclosed in any one of Deboer, Clark, or Lubon. As was discussed in the Prior Reply, Morinaga, which merely discloses the nucleic acid and predicted amino acid sequence of human AFP, does not suggest the expression of rHuAFP in a transgenic non-human mammal under the control of a milk-specific promoter or the secretion of rHuAFP in the milk of that mammal based on the presence of a leader sequence, as is taught in the present specification and recited in present claims 1, 3, 5-7, 10 and 11. Thus, Morinaga fails to provide any motivation to express human AFP using recombinant means of any sort. Because the cited references fail to provide any motivation, suggestion, or teaching of the desirability of making the specific combination that was made by Applicants, a *prima facie* case of obviousness against present claims 1, 3, 5-7, 10, and 11 has not been established. For the reasons given above, the rejection of present claims 1, 3, 5-7, 10, and 11 under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett should be

withdrawn.

Objective Indicia of Nonobviousness

Even if the combination of Deboer, Clark, and Lubon with Morinaga and Bennett did establish a *prima facie* case of obviousness, which it does not, objective indicia can be used to overcome the rejection of present claims 1, 3, 5-7, 10, and 11 under 35 U.S.C. § 103 for obviousness. The M.P.E.P. § 716.01(a) states:

> Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103. The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." Such evidence might give light to circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or unobviousness, such evidence may have relevancy. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966); *In re Palmer*, 451 F.2d 1100, 172 USPQ 126 (CCPA 1971); *In re Fielder*, 471 F.2d 640, 176 USPQ 300 (CCPA 1973).

Applicants again direct the Examiner to ¶ 8 of the Declaration of Mr. Edward J. Stewart, which states that "[t]he high level of rHuAFP expression demonstrated by the transgenic goats far surpasses the level of expression obtained using other expression systems. One of skill in the art would not have expected this level of expression of rHuAFP in a mammal." The amount of rHuAFP expression achieved in Applicants' transgenic mammal expression system (~170-700 mg/L of rHuAFP; see ¶ 7 of the Declaration) is at least two orders of magnitude greater than that achieved using Bennett's bacterial expression system (see page 173, col. 1, of Bennett; "One mg of purified [rAFP] protein was obtained from one liter of bacterial culture."). Thus, Mr. Stewart's statement confirming the unexpected results of rHuAFP expression in transgenic mammals must be

considered as further evidence of the nonobviousness of claims 1, 3, 5-7, 10, and 11. For this reason as well, Applicants respectfully request that the rejection of present claims 1, 3, 5-7, 10, and 11 under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett be withdrawn.

CONCLUSION

Applicants submit that present claims 1, 3, 5-7, 10, and 11 are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including May 1, 2006, as April 30, 2006 fell on a Sunday, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any other charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

TODD ARMSTRONG, Ph.D.
Reg. No. 54,590

Date: 28 April 2006

for Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045